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Usefulness of additional coronary calcium scoring in low-dose CT coronary angiography with prospective ECG-triggering impact on total effective radiation dose and diagnostic accuracy

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Abstract: RATIONALE AND OBJECTIVES: To determine the impact of additional coronary calcium scoring on total effective radiation dose and diagnostic accuracy of low-dose computed tomography coronary angiography (CTCA) with prospective electrocardiogram (ECG) triggering. MATERIALS AND METHODS: Sixty-one consecutive patients underwent 64-slice CTCA using prospective ECG triggering, calcium scoring, and invasive quantitative coronary angiography, the latter served as standard of reference. Diagnostic accuracy was calculated for CTCA, calcium scoring, and for the combination of both. Receiver operator characteristic analyses were performed to determine cutoffs for prediction of significant coronary artery stenoses. RESULTS: Mean effective radiation dose was 2.1 ± 0.7 mSv (range, 1.0-3.3 mSv) for CTCA and 1.1 ± 0.1 mSv (range, 0.9-1.4 mSv) for calcium scoring. Per-patient sensitivity, specificity, positive predictive value, and negative predictive value were 100%, 85.7%, 89.2%, and 100% for CTCA, and 72.7%, 82.1%, 82.8%, and 71.9% for calcium scoring. Adding calcium-scoring with a cutoff at 133 in patients aged >50.7 years with nondiagnostic CTCA improved the respective values of diagnostic accuracy of the entire study population to 100%, 96.4%, 97.1%, and 100%; the added value of calcium scoring was confined to only three patients (5%), who were reclassified from false positive to true negative. CONCLUSION: Specificity and PPV of low-dose CTCA may be further improved by combining it with coronary calcium scoring. However, only a fraction of patient may benefit, whereas exposing the entire population to more than 50% increase in effective radiation dose.

DOI: <https://doi.org/10.1016/j.acra.2009.09.007>

Posted at the Zurich Open Repository and Archive, University of Zurich

ZORA URL: <https://doi.org/10.5167/uzh-32279>

Journal Article

Accepted Version

Originally published at:

Husmann, L; Herzog, B A; Burger, I A; Buechel, R R; Pazhenkottil, A P; von Schulthess, P; Wyss, C A; Gaemperli, O; Landmesser, U; Kaufmann, P A (2010). Usefulness of additional coronary calcium scoring in low-dose CT coronary angiography with prospective ECG-triggering impact on total effective radiation dose and diagnostic accuracy. *Academic Radiology*, 17(2):201-206.

DOI: <https://doi.org/10.1016/j.acra.2009.09.007>

Usefulness of Additional Coronary Calcium Scoring in Low-dose
CT Coronary Angiography with Prospective ECG-Triggering -
Impact on Total Effective Radiation Dose and Diagnostic Accuracy

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Abstract

Rationale and Objectives: To determine the impact of additional coronary-calcium-scoring on total effective radiation dose and diagnostic accuracy of low-dose computed tomography coronary angiography (CTCA) with prospective electrocardiogram (ECG)-triggering.

Materials and Methods: Sixty-one consecutive patients underwent 64-slice CTCA using prospective ECG-triggering, calcium-scoring and invasive quantitative coronary angiography (QCA), the latter served as standard of reference. Diagnostic accuracy was calculated for CTCA, calcium scoring and for the combination of both. Receiver operator characteristic analyses were performed to determine cut-offs for prediction of significant coronary artery stenoses.

Results: Mean effective radiation dose was 2.1 ± 0.7 mSv (range 1.0-3.3 mSv) for CTCA and 1.1 ± 0.1 mSv (range 0.9-1.4 mSv) for calcium-scoring. Per-patient sensitivity, specificity, positive predictive value (PPV), and negative predictive value were 100%, 85.7%, 89.2%, and 100% for CTCA, and 72.7%, 82.1%, 82.8%, and 71.9% for calcium-scoring. Adding calcium-scoring with a cut-off at 133 in patients aged >50.7 years with non-diagnostic CTCA improved the respective values of diagnostic accuracy of the entire study population to 100%, 96.4%, 97.1%, and 100%; the added value of calcium-scoring was confined to only 3 patients (5%), who were reclassified from false positive to true negative.

Conclusion: Specificity and PPV of low-dose CTCA may be further improved by combining it with coronary-calcium-scoring. However, only a fraction of patient may benefit, while exposing the entire population to more than 50% increase in effective radiation dose.

Keywords: prospective ECG-triggering, coronary calcium-scoring, computed tomography coronary angiography, effective radiation dose, diagnostic accuracy

Introduction

Computed tomography coronary angiography (CTCA) with prospective electrocardiogram (ECG)-triggering has recently been introduced and shown to offer a tremendous reduction of radiation dose compared to retrospective ECG-gating (1-6). Hence, a widespread clinical acceptance of non-invasive imaging of the coronary arteries with CTCA may now be envisioned. In selected patient populations with low heart rates, initial reports have demonstrated a high diagnostic accuracy of low dose CTCA with prospective ECG-triggering compared to the current reference standard quantitative coronary angiography (QCA) (7-9), similar to the diagnostic accuracy achieved by retrospective ECG-gating technique (8).

However, the occurrence of artefacts leading to non-diagnostic image quality has been described (2-5, 7-10). When artefacts render CTCA image quality non-diagnostic, patient examinations in clinical routine should be considered as positive and patients should be referred to further clinical work-up, i.e. proof of stress-induced ischemia and/or invasive coronary angiography (ICA). Therefore, depending on the occurrence rate of non-diagnostic image quality, a considerable number of patients will unnecessarily undergo ICA, due to false positive CTCA findings.

The additional use of coronary calcium-scoring has been described to improve diagnostic accuracy of CTCA with retrospective ECG-gating (11-14), especially when used to determine the presence of CAD only in patients with non-diagnostic image quality in CTCA. However, in CTCA with prospective ECG-gating the effective radiation dose has been reduced so much, that the radiation dose of CTCA (in patients with low body mass index) can occasionally equal the radiation dose of a coronary calcium score (15), rendering the usefulness of an additional calcium score questionable.

Therefore, it was the purpose of this study to determine the impact of additional coronary calcium-scoring on total effective radiation dose and diagnostic accuracy of low-dose CTCA with prospective ECG-triggering.

Materials and Methods

Sixty-one consecutive patients with known or suspected CAD scheduled for QCA were prospectively enrolled and underwent an additional CTCA if none of the following exclusion criteria were present: previous stent placement, previous coronary bypass surgery, hypersensitivity to iodinated contrast agent, renal insufficiency (creatinine levels $>150 \mu\text{mol/L}$, or $>1.7\text{mg/dl}$), non-sinus rhythm, acute coronary syndrome, heart rates $>80 \text{ bpm}$ providing there were no contraindications for beta-blocker medication, or heart rates $>65 \text{ bpm}$ when beta-blocker medication was not feasible. Patients were referred because of dyspnoea ($n=12$), typical angina pectoris ($n=35$), atypical chest pain ($n=11$) or because of elevated coronary risk factors ($n=3$).

The study protocol was approved by the institutional review board and written informed consent was obtained from all patients.

All CT examinations were performed on a LightSpeed VCT XT scanner (GE Healthcare). All patients received a single dose of 2.5 mg isosorbiddinitrate sublingual (Isoket, Schwarz Pharma, Monheim, Germany) 2 min prior to the CTCA scanning. In addition, intravenous metoprolol (5 to 20 mg) (Beloc, AstraZeneca, London, UK) was administered prior to the CTCA examination if necessary to achieve a target heart rate $<65 \text{ bpm}$.

Coronary calcium scoring was performed with the following scanning parameters: prospective ECG-triggering, 2.5 mm slice thickness, 120 kV tube voltage, 200 mA tube current, and large scan field-of-view of 50 x 50 cm. For CTCA, 80 ml of iodixanol (Visipaque 320, 320 mg/mL, GE Healthcare, Buckinghamshire, UK) at a flow rate of 5 mL/s (1.6 g iodine/sec) followed by 50 ml saline solution was injected into an antecubital vein via an 18-gauge catheter. CTCA was performed with

prospective ECG-triggering (SnapShot Pulse, GE Healthcare) and the following scanning parameters: bolus tracking in the ascending aorta, collimation 64×0.625 mm, smallest x-ray window (only 75% of the RR-cycle), z-coverage 40 mm with an increment of 35 mm, gantry rotation time 350 ms, temporal resolution 175 ms, body mass index (BMI) adapted tube voltage (100kV: BMI $<25\text{kg/m}^2$, 120 kV: BMI $\geq 25\text{kg/m}^2$) and current (450mA: BMI $<22.5\text{kg/m}^2$, 500mA: BMI $22.5\text{--}25\text{kg/m}^2$, 550mA: BMI $25\text{--}27.5\text{kg/m}^2$, 600mA: BMI $27.5\text{--}30\text{kg/m}^2$, 650mA: BMI $30\text{--}40\text{kg/m}^2$, 700mA: BMI $>40\text{kg/m}^2$). Scanning was performed with a small scan field-of-view of 32×32 cm from below the tracheal bifurcation to the diaphragm, choosing 3 to 5 scan blocks (z-coverage 11 to 18 cm). By choosing the smallest possible window at only one distinct enddiastolic phase of the RR-cycle (i.e. centered at 75%) we ascertained the lowest achievable effective dose delivery, the effective dose of CTCA was calculated as the product of the dose-length product (DLP) times a conversion coefficient for the chest ($k = 0.017 \text{ mSv/mGy} \times \text{cm}$) as previously suggested (16). All images were transferred to an external workstation (AW 4.4, GE Healthcare).

Two independent readers assessed image quality in all coronary segments as “diagnostic” or “non-diagnostic”, for any disagreement in data analysis between the two observers, consensus agreement was achieved.

For analysis of CTCA data, coronary arteries were segmented as suggested by the American Heart Association (17): The right coronary artery (RCA) was defined to include segments 1-4, the left main artery (LM) and the left anterior descending artery (LAD) to include segments 5-10, and the left circumflex artery (CX) to include segments 11-15. The intermedial artery was designated as segment 16, if present. All segments with a diameter of at least 1.5 mm at their origin were included.

Images were evaluated and classified by two independent readers using axial source images, multi-planar reformations, and thin-slab maximum intensity projections on a per-vessel and per-patient basis. Both readers visually assessed all coronary artery segments for the presence of significant stenoses, defined as narrowing of the coronary luminal diameter $\geq 50\%$. Diagnostic accuracy of CTCA was determined on an “intention-to-diagnose”-basis; no coronary segment was excluded; non-evaluative segments were rated as stenosed, as previously suggested (18).

QCA was performed according to standard techniques, and multiple views were stored on a CD-ROM. The angiograms were quantitatively evaluated using QCA software (Xcelera, PhilipsMedical Systems, the Netherlands) by an independent and experienced interventional cardiologist blinded to the results from CT coronary angiography. Coronary artery segments were defined as mentioned above (17), and analysis was performed in all vessels with a luminal diameter of at least 1.5 mm, excluding those vessels distal to complete occlusions. Each vessel segment was scored as being significantly stenosed, defined as a diameter reduction of $\geq 50\%$.

Quantitative variables were expressed as mean \pm standard deviation and categorical variables as frequencies, or percentages. Sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) were calculated; QCA was the standard of reference. The 95% confidence intervals (CI) were calculated from binomial expression per-vessel and per-patient, taking the clustered nature of the data into account (i.e. the 244 examined coronary vessel were not independent but clusters of vessels in 61 patients). Receiver operator characteristic (ROC) analyses were performed to determine patient- and vessel-based cut-offs for prediction of significant coronary artery stenoses (diameter reduction of $\geq 50\%$), and

to determine cut-offs for prediction of false negative findings. A *P*-value of <0.05 was considered to indicate statistical significance. SPSS software (SPSS 15.0, Chicago, ILL, USA) and Stata software (StataCorp 10.0, College Station, USA) were used for statistical testing.

Results

CTCA was successfully performed in all 61 patients; demographics are given in Table 1. Sixteen of 61 patients (26%) were on beta blocker medication as part of their baseline medication; additional intravenous beta blockers were administered for heart rate control prior to CTCA in 35 patients (57%). The mean DLP from calcium-scoring was 63.6 ± 5.8 mGycm (range 54.8-82.0 mGycm) resulting in an estimated mean applied radiation dose of 1.1 ± 0.1 mSv (range 0.9-1.4 mSv); respective values for CTCA were 126.0 ± 42.2 mGycm (range 58.3-193.2 mGycm) and 2.1 ± 0.7 mSv (range 1.0-3.3 mSv).

The overall prevalence of CAD was 54% (33 of 61 patients). For CTCA, per-patient sensitivity, specificity, PPV, and NPV were 100%, 85.7%, 89.2%, and 100%, while the respective vessel-based values were 93.1%, 85.5%, 72.8%, and 96.7% (Table 2). With receiver operator characteristic (ROC) curves cut-off calcium score values of 133 (patient-based) and 57 (vessel-based) were determined ($P < 0.001$) for prediction of significant coronary artery stenoses (Figure 1). For these cut-off values the diagnostic accuracy of coronary calcium-scoring is given in Table 2.

To determine the added value of combining CTCA with calcium-scoring, the latter was used to determine the presence of significant CAD only in patients with non-diagnostic CTCA image quality. With this approach patient-based specificity and PPV were improved (from 85.7% and 89.2% to 96.4% and 96.9%), while, sensitivity and NPV decreased (from 100% and 100% to 93.9% to 93.1%; Table 2).

As significant coronary stenoses may be present especially in younger patients despite zero or low coronary calcium scores (19, 20), any added diagnostic value of calcium-scoring may be age dependent and mostly pronounced in advanced age. In fact, ROC analyses determined cut-off ages of 50.7 ($P < 0.05$) for predicting false negative findings of combined CTCA and calcium-scoring. At this cut-off for the

combined analysis with calcium-score plus CTCA in patients over 51 years with non-diagnostic CTCA image quality results in a per-patient sensitivity, specificity, PPV, and NPV of 100%, 96.4%, 97.1%, and 100% (Table 2). The cut-off age for the per-vessel analysis turned out to be slightly higher, namely at >69 years (area under the curve: 0.91, $P < 0.01$), resulting in similar accuracy values of 93%, 87%, 74%, and 97% (Table 2). Notably, the added value of calcium-scoring was limited to only 3 patients (5%), who were reclassified from false positive to true negative, while the mean effective radiation dose of the entire population increased by 52% (from 2.1 to 3.2 mSv).

Discussion

Low effective radiation dose and high diagnostic accuracy are the main determinants for successful implementation of CTCA in everyday clinical routine. Although CTCA scans with low effective radiation exposure are now feasible with prospective ECG-triggering, non-diagnostic image quality may occasionally still occur (2-5, 7-9) and potentially impair the clinical usefulness of CTCA. Coronary calcium-scoring has been suggested as an adjunct to CTCA with retrospective ECG-gating (11-14), in order to determine the presence of CAD in patients with non-diagnostic image quality in CTCA. The present study shows that an additional coronary calcium-score improves accuracy by increasing specificity and PPV of low-dose CTCA. However, the added value of calcium-scoring was limited to a small fraction of the patients, as only 5% were reclassified from false positive to true negative, at the cost of increasing the mean effective radiation dose of the entire population by 1.1 mSv (52%).

It is important to notice, that the previously suggested cut-offs for the determination of significant CAD are within a range of 130 (11) and 400 (14), which might be caused by differences in the study populations, i.e. age (19, 20) and prevalence of CAD. In our study we found a relatively low prevalence of CAD and a relatively low mean age, most probably contributing to a rather low cut-off at 133.

While the added value of coronary calcium score has been demonstrated with CTCA using retrospective ECG-gating, the present study confirms, that an additional calcium score may also improve the diagnostic accuracy of CTCA using prospective ECG-triggering. However, the latter scanning protocol results in a much lower effective radiation dose to the patient as compared to previous retrospective ECG-gating. Therefore, the balance of harms and benefits of the additional radiation dose by calcium scoring needs to be reevaluated. In fact, the relative increase in total

effective radiation dose to all patients was substantial, to the benefit of only very few patients who were reclassified and in whom ICA would be avoidable. The balance may be favourably shifted to the benefits in patient populations with higher age and minor coronary calcifications (Figure 2).

The usefulness of additional calcium scoring in low-dose CTCA may remain an issue of discussion in the next future, as with the introduction of faster CT scanner systems with larger detector widths encompassing the entire heart, (21) the occurrence of non-diagnostic CTCA image quality (caused by motion or stair-step artefacts) will most likely further decrease, potentially rendering additional coronary calcium scoring redundant. In fact, even with regard to prognosis CTCA may prove superior to coronary calcium-scoring (22).

We acknowledge the following limitations to our study. The ROC curve-determined cut-off ages for identifying false negative findings of combined CTCA and calcium-scoring are based on small numbers, therefore the cut-off value (though statistically significant) must be judged with caution and further studies are required to confirm our findings. As mentioned above, one should be cautious when trying to extrapolate our results to other populations with different demographics, especially age as well as coronary calcium load.

In conclusion, low-dose CTCA with prospective ECG-triggering provides high diagnostic accuracy in the assessment of CAD. Specificity and PPV of low-dose CTCA may be further improved by combining it with coronary calcium-scoring. However, only a fraction of patient may benefit, while exposing the entire population to more than 50% increase in effective radiation dose.

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Figure legends

Figure 1:

Receiver operator characteristic (ROC) curve identifying the cut-off coronary calcium score for prediction of significant coronary artery stenoses (A, patient-based; B, vessel-based). AUC: area under the curve.

Figure 2:

CTCA images demonstrate normal left coronary arteries (A, B, C) but a severe motion artifact in the right coronary artery (arrow heads in E and F) rendering image quality non-diagnostic and the examination positive (intension-to-diagnose). Combining CTCA with coronary calcium score (i.e. 5) allowed to reclassify this 64-year-old patient to be free of coronary artery disease, which was confirmed by invasive coronary angiography (D and G).

Table 1. Patient demographics

Number of patients	61
Age in years (mean \pm SD, range)	61 \pm 11, 30 - 85
Female gender (n)	24
Male gender (n)	37
Body mass index in kg/m ² (mean \pm SD, range)	27 \pm 5, 19 - 45
Heart rate in bpm (mean \pm SD, range)	56 \pm 7, 36 - 70
Coronary risk factors (n)	
Smokers	28
Hypertension	36
Diabetes	4
Positive family history	22
Dyslipidemia	28
Calcium score (mean \pm SD, range)	481 \pm 885, 0 - 5477
Calcium score percentiles (n)	
<25 th percentile	17
25-50 th percentile	8
50-75 th percentile	10
75-90 th percentile	8
>90 th percentile	18

Table 2. Diagnostic accuracy of CTCA, calcium scoring and of the combination of both

		sensitivity	specificity	PPV	NPV
Patient-based	CTCA:	100% (33/33; n.a.)	85.7% (24/28; 67.3-95.9)	89.2% (33/37; 74.6-96.9)	100% (24/24; n.a.)
	Calcium-Score:	72.7% (24/33; 54.5-86.7)	82.1% (23/28; 63.1-93.4)	82.8% (24/29; 64.2-94.2)	71.9% (23/32; 53.3-86.3)
	CTCA plus Calcium-Score:	93.9% (31/33; 79.8-99.3)	96.4% (27/28; 81.6-99.9)	96.9% (31/32; 83.8-99.9)	93.1% (27/29; 77.2-99.2)
	CTCA plus Calcium-Score, patients age >50.7 years:	100% (33/33; n.a.)	96.4% (27/28; 81.7-99.9)	97.1% (33/34; 84.7-99.9)	100% (27/27; n.a.)
Vessel-based	CTCA:	93.1% (67/72; 84.5-97.7)	85.5% (147/172; 79.3-90.4)	72.8% (67/92; 62.6-81.6)	96.7% (147/152; 92.5-98.9)
	Calcium-Score:	70.8% (51/72; 58.9-80.9)	83.7% (144/172; 77.3-88.9)	64.6% (51/79; 53.0-75.0)	87.3% (144/165; 81.2-91.6)
	CTCA plus Calcium-Score combined:	93.1% (67/72; 84.5-97.7)	92.4% (159/172; 87.4-95.9)	83.8% (67/80; 73.8-91.1)	96.9% (159/164; 93.0-99.0)
	CTCA plus Calcium-Score, patients age >68.8 years:	93.1% (67/72; 84.5-97.7)	86.6% (149/172; 80.6-91.3)	74.4% (67/90; 64.2-83.1)	96.8% (149/154; 92.6-98.9)

Numbers in parenthesis correspond to the absolute values and the 95% confidence interval. PPV: positive predictive value. NPV: negative predictive value. NA: not available.